AMENDMENTS TO THE DRAWINGS:

Please replace the Figures 1-3 with the attached Replacement Drawing Sheets. Figures 1, 2 and 3 are each provided on a separate drawing sheet.

Attachment: Replacement Sheets

REMARKS

The Examiner is thanked for the due consideration given the application. Substitute drawing figures are being submitted with this paper.

Claims 1, 2, 4, 5, 7-12, 14, 15, 17, 19 and 21-24 are pending in the application. Claims 11, 12 and 24 have been withdrawn from consideration.

The Drawings

The drawing figures have been objected to. Replacement drawing figures have been supplied with this paper in which each of Figures 1, 2 and 3 appears on a separate sheet.

Rejection Under 35 USC §103(a)

Claims 1, 2, 4, 5, 7-10, 14, 15, 17, 19 and 21-23 have been rejected under 35 USC §103(a) as being unpatentable over ZURBRIGGEN et al., CULLIS et al., GLUCK and METCALF and JIRA and JIRATHITIKAL. This rejection is respectfully traversed.

The present invention relates to a reconstituted viral membrane, the lipid bilayer of which comprises a fusion protein of a virus, an amphiphilic adjuvant and, optionally a further antigen, whereby:

(a) the lipid bilayer has a lipid composition that is compatible with fusion, induced by the fusion protein, of the viral membrane with the membrane of a cell that can be fused with the virus from which the fusion protein is derived;

(b) the fusion protein and the amphiphilic adjuvant interact with the hydrophobic interior of the lipid bilayer; and,

(c) the fusion protein, the amphiphilic adjuvant and the optional further antigen are not covalently linked; and wherein the amphiphilic adjuvant is a lipopeptide. Preferably, the amphiphilic adjuvant is the lipopeptide N-palmitoyl-S-2,3 (bisoleoyloxy)-propyl-cysteinyl-seryl-(lysil)3-lysine (mentioned in claim 5) and not N-palmitoyl-S-2,3(bisoleoyloxy)-propyl-cysteinyl-seryl-serine as is mentioned in the Office Action. In fact, the latter is not mentioned in the patent application.

The present invention also pertains to a pharmaceutical composition (claims 14 and 15) of a reconstituted viral membrane.

ZURBRIGGEN et al.

Applicant disagrees with the assertion that PC and PR in ZURBRIGGEN et al. provide an adjuvant effect as part of the viral envelope. ZURBRIGGEN et al. do not disclose that PC and PE have an adjuvant effect. In addition, since PC and PE are the body's own substances, they are highly unlikely to have an adjuvant effect. Analysis of scientific literature did not reveal any support for the assertion that PC and PE have an adjuvant effect. Thus, ZURBRIGGEN et al. teach reconstituted influenza virosomes (TRW) which contain HA and NA from influenza viral particles and PC and PE. Nevertheless, ZURBRIGGEN et al. do not disclose IRIVs comprising an amphiphilic adjuvant.

CULLIS et al.

CULLIS et al. discloses a pharmaceutical composition for introducing a therapeutic compound into a cell of a host, the pharmaceutical composition including: a liposome containing a lipopeptide, the lipopeptide including a lipid covalently attached to a peptide by means of an amide bond; a therapeutic compound contained in the liposome; and a pharmaceutically acceptable carrier (column 3, lines 18-25). Thus, CULLIS et al. does not relate to raising an immune response to an antigen or to a vaccine, nor does the composition include a reconstituted viral membrane or a fusion protein of a virus.

In column 3, lines 54-60, CULLIS et al. disclose a composition comprising a virosome having a membrane and an aqueous interior, where HA is contained in the membrane, and further including a therapeutic compound contained in the virosome and a pharmaceutically acceptable carrier. Thus, here the composition is not related to raising an immune response to an antigen or to a vaccine, nor does it comprise an amphiphilic adjuvant.

CULLIS et al. disclose a virosome composition, including viral membrane fusion protein (HA) and a therapeutic compound (column 31, line 66 – column 36, line 47).

Since CULLIS et al. is directed at delivery of a therapeutic compound in a cell and not at raising an immune response or vaccination, the skilled person would not combine

CULLIS et al. and ZURBRIGGEN et al. Even if the skilled person would combine these documents, he would not arrive at the invention, since CULLIS et al. teach that the peptides used to form the lipopeptides must have a ***fusogenic function***: "the peptide used to form the lipopeptide can be any peptide known to promote membrane fusion" (column 16, lines 58-59). Fusogenic peptides can be derived from known viral fusion proteins, e.g., the viral fusion protein of influenza HA (column 16, lines 65-67).

In addition, there is no teaching in CULLIS et al. that a lipopeptide can be used as amphiphilic adjuvant. In contrast to CULLIS et al., the present invention uses a fusion protein (preferably HA, NA or an M2 protein) for fusion, whereas a lipopeptide is used as an amphiphilic adjuvant. From the disclosure of CULLIS et al., the skilled person would not expect that a lipopeptide could be used to improve the immune response following administration of a reconstituted viral membrane comprising a fusion protein of a virus. In fact, the lipoproteins that are disclosed by CULLIS et al. (paragraph 16, line 58 - paragraph 18, line 49) are not capable of acting as an amphiphilic adjuvant.

GLUCK & METCALFE

GLUCK & METCALFE disclose immunopotentiating reconstituted influenza virosomcs (IRIVs), which contain intercalated influenza HA and NA on its surface, ***co-administered***

with an additional mucosal adjuvant (page 614, left column, last two lines), *E. coli* heat-labile toxin (HLT). Thus, the mucosal adjuvant is not part of the reconstituted viral membrane. HLT is neither an amphiphilic adjuvant nor a lipopeptide. Since HLT is a water soluble protein, it is not capable of association with a reconstituted viral membrane.

Therefore, also GLUCK & METCALFE do not disclose a reconstituted viral membrane comprising an amphiphilic adjuvant, where the amphiphilic adjuvant is a lipopeptide. Thus, the skilled person combining ZURBRIGGEN et al., CULLIS et al. and GLUCK & METCALFE would not produce a claimed embodiment of the present invention. As noted above, the skilled person would not have an incentive to combine ZURBRIGGEN et al. and CULLIS et al. in the first place. In addition, the skilled person would not have any expectation of success that a lipopeptide could be used to improve the immune response following administration of a reconstituted viral membrane including a fusion protein of a virus.

JIRA & JIRATHITIKAI

JIRA & JIRATHITIKAI pertain to a composition comprising a first component comprising denatured antigen of an infection-inducing pathogen and a second component formed from denatured tissue derived from a pathogen-infected animal. In paragraph 101 JIRA & JIRATHITIKAI discuss that a typical carrier and adjuvant is N-palmitoyl-S-2,3(bispalmitoyloxy)-propyl-cysteinyl-seryl-

serine. Further, JIRA & JIRATHITIKAI use recombinant chimeric viruses, e.g., human rhinovirus 14 into which chimeric regions derived from influenza HA are incorporated (paragraph 81).

However, JIRA & JIRATHITIKAI do not disclose a reconstituted viral membrane. HA, NA and NP are disclosed to be suitable antigens (paragraph 22). Since JIRA & JIRATHITIKAI do not relate to reconstituted viral membranes, the skilled person would not combine ZURBRIGGEN et al., CULLIS et al. and GLUCK & METCALFE with JIRA & JIRATHITIKAI in the first place. If the skilled person would make the combination then he would still not arrive at the invention, since there is no indication in JIRA & JIRATHITIKAI that the carriers and adjuvants mentioned in paragraph 101 should be intercalated in a membrane.

Moreover, there is no suggestion that provides the skilled person in the art with a reasonable expectation of success that a lipopeptide would be required, since most of the substances in the list of paragraph 101 of JIRA & JIRATHITIKAI do not belong to the group of lipopeptides and, in addition, could thus not be used to achieve the present invention.

As a result, one of ordinary skill and creativity would fail to produce a claimed embodiment of the present invention from a knowledge of the applied art references, and a *prima facie* case of unpatentability has thus not been made.

Further, the present invention shows results that are unexpected in light of the various references of ZURBRIGGEN et

al., CULLIS et al. and GLUCK & METCALFE with JIRA & JIRATHITIKAI. These results are typified by the Examples described in the specification and the associated drawing figures, where the present invention shows improved performance when compared to the related art of, e.g., EP 0583437. The advantages of the present invention are thus clear.

This rejection is believed to be overcome, and withdrawal thereof is respectfully requested.

Election/Restriction

As allowable subject matter has been indicated, the Examiner is respectfully requested to re-join the pending withdrawn claims.

Conclusion

The Examiner is thanked considering the Information Disclosure Statements filed December 13, 2005 and November 18, 2008, and for making the initialled PTO 1449 forms of record in the application.

Prior art of record but not utilized is believed to be non-pertinent.

The objections and rejections are believed to be overcome, obviated or rendered moot, and no issues remain. The Examiner is accordingly respectfully requested to place the application in condition for allowance and to issue a Notice of Allowability.

Should there be any matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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APPENDIX:

The Appendix includes the following item(s):

☒ - Replacement Sheets for drawings